



PCT/GB 2004/00235



GB0410935A

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

REC'D 21 JUL 2004

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

**PRIORITY
DOCUMENT**

SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (b)

Signed

Dated

R. Mahoney
23 June 2004

BEST AVAILABLE COPY

1/77
03 JUN 03 0811882-001891
P01/7700 0.00-0312642.2**Request for grant of a patent***(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)*THE PATENT OFFICE
B
03 JUN 2003
NEWPORT

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference

P1362

2. Patent application number

(The Patent Office will fill in this part)

03 JUN 2003

0312642.2

3. Full name, address and postcode of the or of
each applicant *(underline all surnames)*THE SECRETARY OF STATE FOR DEFENCE
DSTL
Porton Down
Salisbury. Wiltshire. SP4 0JQ

06997670005

Patents ADP number *(if you know it)*If the applicant is a corporate body, give the
country/state of its incorporation

GB

4. Title of the invention

Pharmaceutical Composition

5. Name of your agent *(if you have one)*Beckham Robert William"Address for service" in the United Kingdom
to which all correspondence should be sent
*(including the postcode)*D/IPR Formalities Section
Poplar 2
MoD Abbey Wood #2218
Bristol
BS34 8JH. UKPatents ADP number *(if you know it)*

08534588001

6. If you are declaring priority from one or more
earlier patent applications, give the country
and the date of filing of the or of each of these
earlier applications and *(if you know it)* the or
each application number

Country

Priority application number
*(if you know it)*Date of filing
*(day / month / year)*7. If this application is divided or otherwise
derived from an earlier UK application,
give the number and the filing date of
the earlier application

Number of earlier application

Date of filing
*(day / month / year)*8. Is a statement of inventorship and of right
to grant of a patent required in support of
this request? *(Answer 'Yes' if:*

Yes

- a) any applicant named in part 3 is not an inventor, or
- b) there is an inventor who is not named as an applicant, or
- c) any named applicant is a corporate body.

See note (d))

9. Enter the number of sheets for any of the following items you are filing with this form.
Do not count copies of the same document

Continuation sheets of this form

Description	12
Claim(s)	3
Abstract	1
Drawing(s)	3

+ 3

PR

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77)

Yes (1)

PR

Request for substantive examination (Patents Form 10/77)

Any other documents
(please specify)

11. I / We request the grant of a patent on the basis of this application.

Signature

Dr N A Riddle

Date 02 June 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

Miss Laura Morrison 0117 91 30228

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent of the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

- a) If you need help to fill in this form or have any questions, please contact the Patent Office on 0645 500505.
- b) Write your answers in capital letters using black ink or you may type them.
- c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
- d) If you have attached 'Yes' Patents Form 7/77 will need to be filed.
- e) Once you have filled in the form you must remember to sign and date it.
- f) For details of the fee and ways to pay please contact the Patent Office.

Pharmaceutical composition

The present invention relates to pharmaceutical compositions containing combinations of antibody fragments, useful in the 5 treatment of various conditions and in particular in the treatment of conditions caused by toxins. Methods of treatment utilising these compositions form a further aspect of the invention.

10 The concept of using animal or human-derived polyclonal antibodies and antidotes or antisera against toxins is well established. The British Pharmacopoeia lists antisera against a number of venoms and toxins produced by micro-organisms, as well as poisonous animals such as snakes and scorpions.

15 The antisera are obtained by fractionation of the serum of horses or other mammals that have been immunised against the toxin of interest. In general, the active component of the antiserum consists of whole antibodies (e.g. IgG, IgT) although in recent 20 years, there has been a move towards the use of despeciated antibody fragments such as $F(ab)_2$ and $F(ab')_2$.

These fragments have the advantage of producing fewer side effects in the patients, and thus an improvement in safety.

25 When dealing with the victims of some toxin intoxication however, there is a very short window of opportunity during which any medical countermeasures are effective.

30 The present invention provides a pharmaceutical composition comprising (i) a first specific binding agent selected from an antibody or a large binding fragment of an antibody which specifically binds a target toxin, and (ii) a second specific binding agent which comprises a small binding fragment of an 35 antibody which binds said toxin.

Compositions of the invention have been found provide rapid and sustained antitoxin activity. This may be due to the fact that the compositions are able to produce an effect, which utilises the mutually complementary properties of the first and second 5 specific binding agents to provide sustained antitoxin capability.

One factor that affects the window of opportunity in the treatment of toxin intoxication is the speed with which the 10 antitoxin is distributed around the body to the sites of action of the toxin. Molecules of the first specific binding agent appear to be less extensively distributed into the extravascular space than molecules of the second specific binding agent. The second specific binding agent appears to provide an antitoxin 15 capability that penetrates rapidly into the extravascular space to provide rapid protection.

The binding of antibodies such as IgG and fragments to toxins is reversible, and therefore there is a risk of a "rebound" effect 20 due to toxin being released, unless at least some functional antibody or antibody fragment remains in the plasma to bind any released toxin. Rapid clearance of the smaller molecules of the second specific binding agent may mean that they are less available in the plasma to "mop up" released toxin. However, by 25 virtue of their slower clearance and higher residual plasma level, the first specific binding agent may bind any toxin released and thereby minimise the rebound effect. In addition, they provide prolonged protection by virtue of their lower clearance rate.

30 The first and second binding agents may bind the same or different antigens provided they are associated with the same toxin.

35 Suitably they have an inactivating effect on the toxin, and prevent the toxin from entering cells.

As used herein, the term "toxin" includes poisons and venoms produced by living organisms, such as bacteria, plants, snakes or insects such as scorpions. It may also include synthetic poisons.

5

The first specific binding agent may comprise an antibody such as an immunoglobulin, which may be IgG, IgM, IgE, IgA, IgD or any subclass thereof, but in particular is an IgG or IgT. The dosages of first specific binding agent required in a composition 10 of the invention is lower than would be required conventionally and therefore adverse side effects or reactions, such as the possibility of anaphylactic shock, may be reduced or minimised. However, if desired the antibody may be "humanised" using conventional methods, or comprise a chimeric antibody.

15

In particular however, the first specific binding agent comprises a large binding fragment of an antibody.

As used herein the expression "large binding fragment" refers to 20 an antibody fragment that comprises a significant proportion of the antibody from which it is derived. For instance, it will comprise the entire variable domain, as well as some of a constant region (Fc). In particular, large antibody fragments include $F(ab')_2$ or $F(ab)_2$ fragments, but they may also comprise 25 deletion mutants of an antibody sequence.

In particular the first specific binding agent comprises a large binding fragment selected from $F(ab')_2$ or $F(ab)_2$ fragments. The acronyms used here are conventional in the art and are understood 30 by a skilled person.

The expression "small binding fragment" refers to an antibody fragment which lacks a significant element of the antibody from which it is derived, for instance, it may lack a significant 35 proportion of the Fc chain, provided it retains its ability to bind the toxin. In particular, small antigen binding fragments

include Fab or Fab' fragments, as well as single chain (sc) antibodies, FV, VH or VK fragments.

5 In particular the second specific binding agent comprises a small binding fragment selected from Fab or Fab' fragments.

Preferably at least one of the first or second specific binding agents will include a section corresponding to part of the Fc region of the antibody.

10 Antibodies used in the compositions of the invention, or from which the large and small binding fragments are derived may be polyclonal or monoclonal, which may be produced using conventional methods.

15 For instance, polyclonal antibodies may be generated by immunisation of an animal (such as a rabbit, rat, goat, horse, sheep etc) with the toxin or immunogenic subunits or fragments thereof, to raise antisera, from which antibodies may be 20 purified.

Monoclonal antibodies may be obtained by fusing spleen cells from an immunised animal such as with hybridoma cells, and selecting cells which secrete suitable antibodies.

25 Antibody binding fragments for use in the compositions, whether large or small, are suitably derived from polyclonal or monoclonal antibodies using conventional methods such as enzymatic digestion with enzymes such as papain or pepsin (to produce Fab and $F(ab')_2$ fragments respectively). Alternatively, 30 they may be generated using conventional recombinant DNA technology.

35 Small and large antigen binding fragments used in the composition of the invention may be derived from the same or different sets or source of antibody. They may be specific for the same or

different antigens, provided that the antigens are associated with the same toxin.

In particular the antigen is associated with a toxin which is required to be inactivated in a patient. The toxin may be present as a result of exposure to the toxin. For example toxins such as botulinum toxin, anthrax toxin or plant derived toxins such as ricin toxin, may be inhaled in biological warfare situations or in laboratory accidents, or they may be ingested in food containing them. The latter also applies to *Staphylococcal* enterotoxins, which are typically associated with food poisoning. Alternatively, toxins may be produced as a result of infection with an organism. Particular organisms known to produce toxins include *C.botulinum*, such as is found in wound botulism or infant botulism, clostridial species in general, for example *C. perfringens*, *C. bifermentans*, *C. difficile* or *C. tetani*, *Staphylococcus* species and *Bacillus anthracis* which produces anthrax toxins.

In particular, the antigen is associated with a botulinum toxin, which may be any of type A, B, C, D, E, F or G.

Compositions of the invention may comprise first and second specific binding agents, which bind more than one toxin molecule, for example, a range of toxins produced by the same microorganism or animal. Thus the specific binding agents may be multivalent in nature, or they may be specific for antigens which are common to more than one toxin. Alternatively, the compositions may comprise more than one "set" of first and second specific binding agents, each set being specific for a different toxin molecule.

In a particular embodiment, the composition of the invention comprises two "sets" of first and second specific binding agents, each set binding a different botulinum toxin A, B, C, D, E or F. Preferably at least three sets of first and second specific binding agents are present, and most preferably, sets of specific

binding agents which are specific for all of toxins A-F are included.

Suitably, in each case, the ratio of the first specific binding agent to the second specific binding agent is in the w/w ratio of 5 90:10 to 10:90, more suitably from 70:30 to 30:70 or and preferably from 60:40 to 40:60.

Compositions of the invention may further comprise 10 pharmaceutically acceptable carriers or excipients as are well known in the art. They may be solid or liquid carriers depending upon the intended mode of administration.

Any desired mode of administration may be used, and this will 15 depend upon factors such as the nature of the toxin being treated, and the nature of the patient. In particular compositions of the invention will be intended for oral, parenteral (especially intravenous) or intranasal administration, or for administration by inhalation or insufflation.

20 Oral compositions may be in the form of tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs. Compositions for parenteral administration will suitably be in the form of a 25 sterile aqueous or oily solution for intravenous, subcutaneous, or intramuscular dosing.

Compositions for intranasal administration or for administration 30 by inhalation or insufflation will suitably comprise a finely divided powder, and inhalable compositions may also be in the form of a liquid aerosol.

Compositions of the invention may comprise other components such 35 as preservative agents, inert diluents, granulating and disintegrating agents, binding agents, lubricating agents,

anti-oxidants as well as colouring, sweetening or flavouring agents, depending upon the nature of the composition.

Compositions for administration by inhalation may be in the form
5 of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a
10 metered quantity of active ingredient.

The relative amounts of pharmaceutically acceptable carrier to the first and second binding agents in a formulation will vary depending upon factors such as the particular route of
15 administration. Generally however, compositions will comprise from about 1 to about 98 percent by weight of pharmaceutically acceptable carrier, and preferably from 5 to 90 percent by weight of pharmaceutically acceptable carrier.

20 The size of the dose for therapeutic purposes of a composition of the invention will naturally vary according to the nature and severity of the condition, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine. Generally however, patients are given
25 from 0.5 mg to 75 mg per kg body weight of the first and second binding agents.

Compositions of the invention are suitably administered to a patient in need thereof, as soon as possible after exposure to
30 the toxin. In the case of a poisoning incident, such as a snake or scorpion bite, this may be carried out as soon as possible after the incident has occurred. In the case of toxins produced by microorganisms, which have infected a patient and where exposure is not known of, the compositions are suitably
35 administered as soon as symptoms are noted.

Early administration of the composition of the invention is particularly effective, as the inclusion of the second binding agent results in fast inactivation of toxin molecules, which may prevent the toxin entering cells, to cause irreparable damage.

5 The window of opportunity will vary depending upon the particular patient or animal exposed, and the dosage of the toxin.

In a further aspect, the invention provides a combination of (i) a first specific binding agent selected from an antibody or a 10 large binding fragment of an antibody which specifically binds a target toxin, and (ii) a second specific binding agent which comprises a small binding fragment of an antibody which binds said toxin, for use in the treatment of the effects of the toxin.

15 Thus in yet a further aspect, the invention provides the use of a combination of (i) a first specific binding agent selected from an antibody or a large binding fragment of an antibody which specifically binds a target toxin, and (ii) a second specific binding agent which comprises a small binding fragment of an 20 antibody which binds said toxin, in the preparation of a medicament for the treatment of the effects of the toxin.

The invention further comprises a method of preventing the effects of a toxin on a mammal such as a human, said method 25 comprising administering to a mammal in need thereof, a composition as described above.

The composition is suitably administered as soon as possible after the toxin has entered the mammal's body, either as a result 30 of a poisoning incident or as a result of infection with a microorganism, which produces a toxin. Repeat administrations using the administration methods and dosages in accordance with standard clinical practice, may be necessary.

The invention will now be particularly described by way of example with reference to the accompanying diagrammatic drawings in which:

5 Figure 1 shows a summary of the results of a range of therapies including those of the invention on the symptoms observed in mice to which the therapies were administered 30 minutes after exposure to Type A botulinum toxin (100MLD₅₀);

10 Figure 2 illustrates the mean symptoms score produced following administration of compositions comprising varying amounts of the components of the compositions of the invention to mice 20 minutes after exposure to Type A botulinum toxin (100MLD₅₀);

15 Figure 3 shows a comparison of symptoms of botulinum intoxication in surviving mice following post-exposure therapy with individual antitoxin fragments or combinations.

Example 1

20 Studies were carried out to investigate the effectiveness of goat derived polyclonal antisera raised against toxoids of botulinum toxin (types A to E). The antisera was purified to whole IgG and its fragments F(ab')₂, Fab' and Fab using conventional methods.

25 Balb/c mice (6 per group) were given type A botulinum toxin (100MLD₅₀) intraperitoneally. Thirty minutes later, antitoxin treatment consisting of antibodies, or fragments or combinations were administered intravenously. Treatment groups consisted of:

1. IgG (2mg)
2. F(ab')₂ (1.6mg)
3. IgG (1mg) + Fab (0.8mg)
4. IgG (1mg) + F(ab')₂ (0.8mg)
5. F(ab')₂ (0.8mg) + F(ab) (0.8mg)
6. F(ab')₂ (0.8mg) + F(ab') (0.8mg)
- 35 7. F(ab') (1.6mg)
8. Fab (1.6mg)

Thus, when given as combinations, the doses of each were reduced to maintain equimolar doses of antigen recognition sites. The ability of the individual fragments and combinations to protect mice from death and also to reduce symptoms of intoxication was 5 monitored. Symptom scores were calculated as follows:

10 1= increased rate of breathing
2= 1 + slight pinching of abdomen
3= 1 + medium pinching of abdomen
4= 1 + medium pinching of abdomen + pilo erection.

The symptom scores (mean per group) at various times measured at 6, 24, 48 and 72 hours after administration are shown in Figure 1. The Fab fragment alone was unable to prevent death.

15 It was found that, when administered as individual fragments, IgG, $F(ab')_2$ and Fab' were equally effective at preventing death. However, the combinations of fragments gave better protection against the development of symptoms.

20 The graph of Figure 1 shows that the combination of $F(ab')_2$ with either Fab or $F(ab')$ gave a reduction in the severity of symptoms observed at various time points during the next few days compared to other combinations or fragments alone. All animals went on to 25 fully recover.

Example 2

Variation in composition of the combination

30 In order to determine the effect of altering the ratio of $F(ab')_2$ and Fab' on prevention of development of symptoms of intoxication in mice following toxin administration, $F(ab')_2$ and Fab' were administered intravenously in varying proportions, with a total dose always of 1.6mg, 20 minutes after intraperitoneal administration of $100MLD_{50}$ of type A botulinum toxin. Again 35 symptoms were recorded at various times using the symptom scoring route

- 1 = increased rate of breathing
- 2 = 1 + slight pinching of abdomen

The group means are shown in Figure 2.

5

It is clear that the combinations were all better than the individual fragments alone. Furthermore, complete prevention of symptoms was possible using a combination of $F(ab')_2$ and Fab' administered within the early window of opportunity (i.e. within 10 20 minutes of exposure), and prevent any symptoms developing compared to mild symptoms developing with the fragments when used alone. This was achieved using relative proportions of the fragments in the range of from a 6:4 mixture to a 4:6 mixture.

15 Example 3

Investigation of the therapeutic window

Although it was found that the combination of the invention did not generally lengthen the therapeutic window (results not shown), if administered early, the combination of the invention 20 did lead to a reduction in symptoms.

Groups of six balb/c mice were dosed intravenously with one of the following treatment regimes:

25 1. $F(ab')_2$ (1.6mg)
2. $F(ab')_2$ (0.8mg) + Fab' (0.8mg)
3. Fab' (1.6mg)

at various time points (60, 75, 90 or 240 minutes) following ip. 30 administration of 10 MLD_{50} type A botulinum toxin. Symptoms of individual mice were scored 24 hours later using the scoring scale described in Example 1 above. The mean score per group per time point are shown in Figure 3A.

35 The experiment was repeated, but on this occasion, the mice were given 100 MLD_{50} type A botulinum toxin and the antitoxins were

given at either 20, 30 or 60 minutes later. Symptoms of individual mice were scored 24 hours later using the scoring scale described in Example 1 above. The mean score per group per time point are shown in Figure 3B.

5

These results suggest that beyond a certain time point following exposure enough toxin has entered the cells to cause irreparable damage and no therapy can be successfully reverse these effects. If given early enough, the fragments can prevent the emergence of 10 any symptoms of intoxication, but the effect of the combination is better.

However at interim time points, symptoms of intoxication are apparent although the animals usually recover fully. At early 15 and interim time points, the use of a combination of antitoxin fragments produced clear superiority in the reduction of the severity of symptoms that develop in comparison to the fragments or IgG administered alone. This is an important finding as the milder the symptoms the less incapacitating the illness is.

20

Claims

1. A pharmaceutical composition comprising (i) a first specific binding agent selected from an antibody or a large binding fragment of an antibody which specifically binds a target toxin, and (ii) a second specific binding agent which comprises a small binding fragment of an antibody which binds said toxin.
2. A composition according to claim 1 wherein the first specific binding agent comprises a large binding fragment of an antibody.
3. A composition according to claim 2 wherein the large binding fragment of an antibody is a $F(ab')_2$ or $F(ab)_2$ fragment.
4. A composition according to claim 1 wherein the first specific binding agent is an antibody which is an IgG or IgT.
5. A composition according to claim 4 wherein the antibody is humanised.
6. A composition according to any one of the preceding claims wherein the second specific binding agent comprises an Fab, Fab', a single chain (sc) antibody or an FV, VH or VK fragment.
7. A composition according to claim 6 wherein the second specific binding agent comprises Fab or Fab' fragment.
8. A composition according to any one of the preceding claims wherein the first and/or second binding agents are derived from polyclonal antibodies.
9. A composition according to any one of claims 1 to 7 wherein the first and/or second binding agents are derived from monoclonal antibodies.

10. A composition according to any one of the preceding claims wherein at least one of the first or second specific binding agents includes a section corresponding to part of the Fc region of an antibody.

5

11. A composition according to any one of the preceding claims wherein the toxin is a Botulinum toxin.

10 12. A composition according to claim 11 wherein the first and second specific binding agents bind at least one of type A, B, C, D, E, F or G botulinum toxin.

15 13. A composition according to claim 12 wherein the composition comprises sets of first and second specific binding agents each set of specific binding agents binding a different one of botulinum toxins A, B, C, D, E, F or G.

20 14. A composition according to any one of the preceding claims wherein the w/w ratio of the first specific binding agent to the second specific binding agent is in the range of from 90:10 to 10:90.

25 15. A composition according claim 14 wherein the w/w ratio of the first specific binding agent to the second specific binding agent is in the range of from 70:30 to 30:70.

30

16. A composition according to claim 15 wherein the w/w ratio of the first specific binding agent to the second specific binding agent is in the range of from 60:40 to 40:60.

17. A composition according to any one of the preceding claims which further comprises a pharmaceutically acceptable carrier or excipient.

35 18. A composition according to any one of the preceding claims which is suitable for oral, parenteral, or intranasal

administration, or for administration by inhalation or insufflation.

19. A combination of (i) a first specific binding agent
5 selected from an antibody or a large binding fragment of an antibody which specifically binds a target toxin, and (ii) a second specific binding agent which comprises a small binding fragment of an antibody which binds said toxin, for use in the treatment of the effects of the toxin.

10
20. The use of a combination of (i) a first specific binding agent selected from an antibody or a large binding fragment of an antibody which specifically binds a target toxin, and (ii) a second specific binding agent which comprises a small binding fragment of an antibody which binds said toxin, in the preparation of a medicament for the treatment of the effects of the toxin.

15
20
21. A method of preventing the effects of a toxin on a mammal such as a human, said method comprising administering to a mammal in need thereof, a composition according to any one of claims 1 to 18.

25
21. A composition substantially as hereinbefore described.

Abstract**Pharmaceutical composition**

5 A pharmaceutical composition comprising (i) a first specific binding agent selected from an antibody or a large binding fragment of an antibody which specifically binds a target toxin, and (ii) a second specific binding agent which comprises a small binding fragment of an antibody which binds said toxin.

10

The compositions are used in the treatment of toxin poisoning, for example following exposure to toxins such as Botulinum toxins.

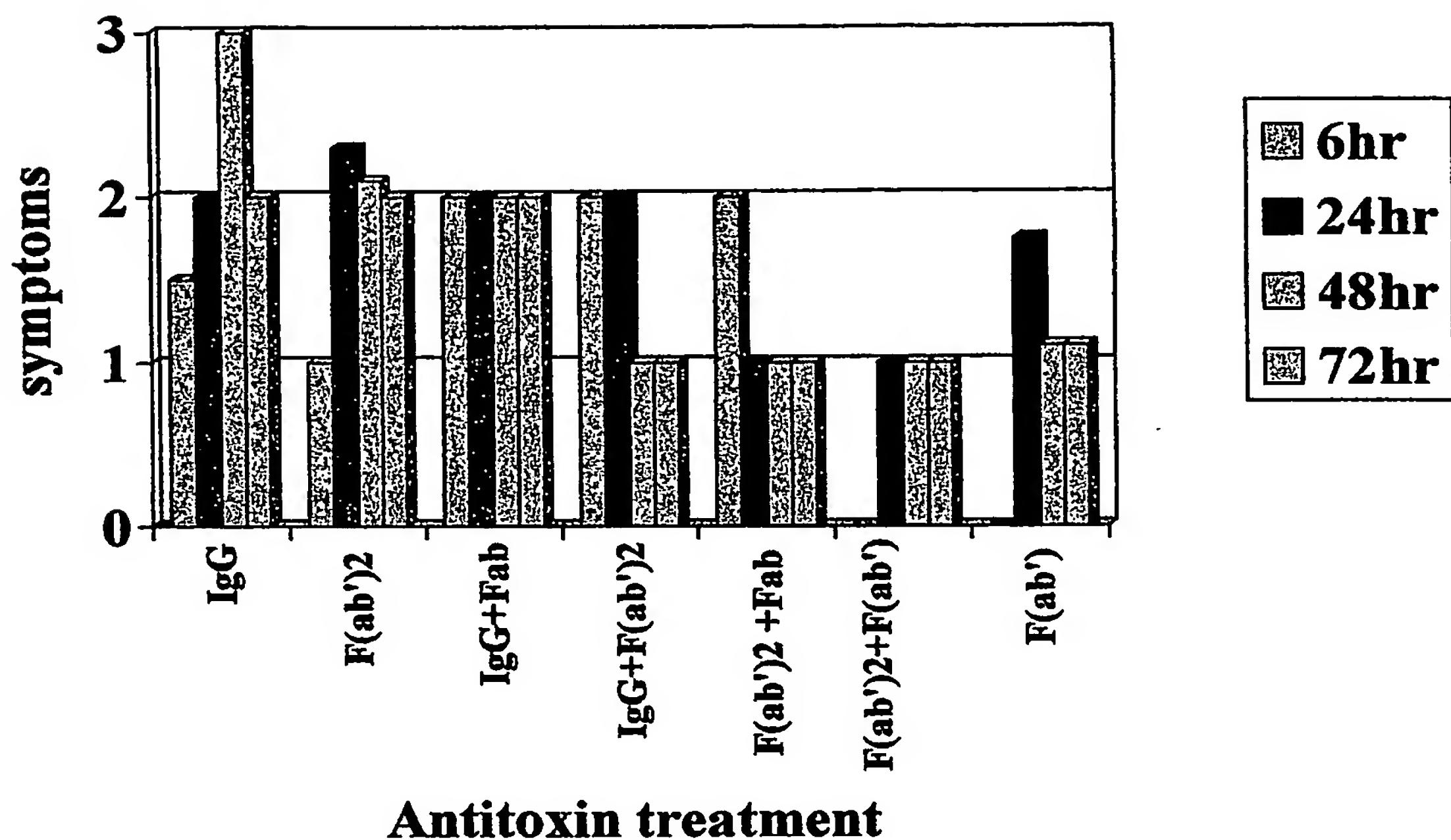
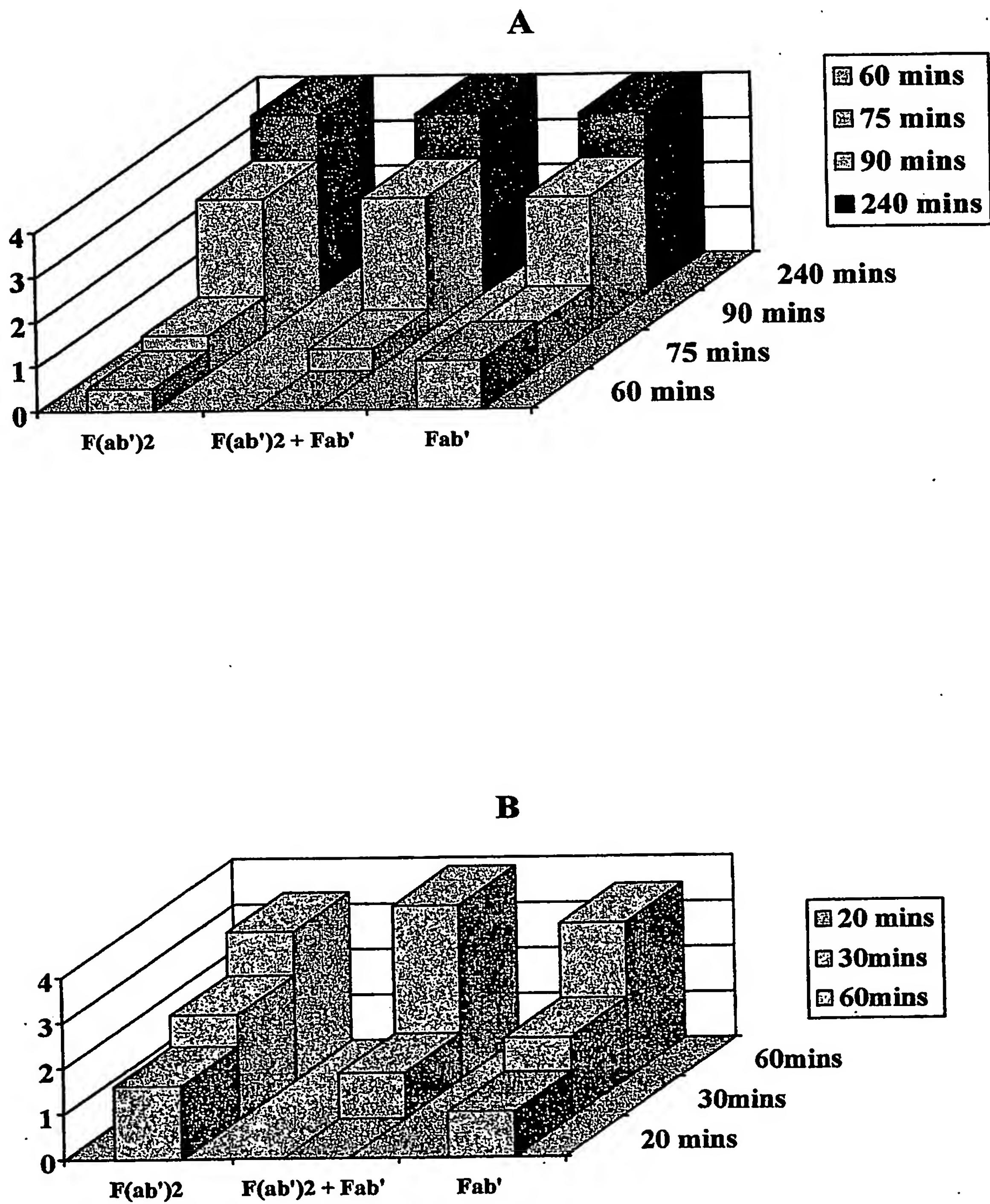
Figure 1

Figure 3



**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.